Analysis of drug-drug interactions in Swiss claims data using tizanidine and ciprofloxacin as a prototypical contraindicated combination

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Abstract: BACKGROUND: Potential drug-drug interactions (pDDIs) are described in various case reports, but few studies have evaluated the impact of specific combinations on a population level. OBJECTIVE: To analyze the type and frequency of multiple contraindicated (X-pDDIs) and major interactions (D-pDDIs) and to subsequently assess the impact of the particular combination of tizanidine and ciprofloxacin on outpatient physician visits and hospitalizations. METHODS: Anonymized Swiss claims data from 524 797 patients in 2014-2015 were analyzed. First, frequencies of X- and D-pDDIs were calculated. Next, a retrospective cohort study was conducted among patients prescribed tizanidine and ciprofloxacin (exposed, n = 199) or tizanidine and other antibiotics (unexposed, n = 960). Hospitalizations and outpatient physician visits within 7, 14, and 30 days after initiation of antibiotic therapy were evaluated using multiple binary logistic regression and multiple linear regression. RESULTS: The relative frequencies of X- and D-pDDIs were 0.4% and 6.65%, respectively. In the cohort study, significant associations between exposure to tizanidine and ciprofloxacin and outpatient physician visits were identified for 14 and 30 days (odds ratio [OR] = 1.61 [95% CI = 1.17-2.24], P = 0.004, and OR = 1.59 [95% CI = 1.1-2.34], P = 0.016). A trend for increased risk of hospitalization was found for all evaluated time periods (OR = 1.68 [95% CI = 0.84-3.17], OR = 1.52 [95% CI = 0.63-3.33], and OR = 2.19 [95% CI = 0.88-5.02]). CONCLUSION and RELEVANCE: The interaction between tizanidine and ciprofloxacin is not only relevant for individual patients, but also at the population level. Further investigation of the impact of other clinically relevant DDIs is necessary to improve patient safety and reduce avoidable health care utilization.

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Impact of the Interaction between Tizanidine and Ciprofloxacin on Healthcare Utilisation in Swiss Claims Data

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Abstract

Background: Potential drug-drug interactions (pDDI) are well described in various case reports, but few studies have evaluated the impact of single combinations on a population level.

Objective: To analyse type and frequency of contraindicated (X-pDDI) and major interactions (D-pDDI). In addition, we assess the impact of the combination of tizanidine and ciprofloxacin on outpatient physician visits and hospitalisations.

Methods: Anonymised Swiss claims data from 524,797 patients in 2014-2015 was analysed. Frequencies of X- and D-pDDI were calculated. A retrospective cohort study was conducted for patients with tizanidine and ciprofloxacin (exposed, n = 199) and patients prescribed tizanidine and other antibiotics (unexposed, n = 960). Hospitalisations and outpatient physician visits within 7, 14 and 30 days after initiation of antibiotic therapy were evaluated using multiple binary logistic regression and multiple linear regression.

Results: The relative frequencies of X- and D-pDDI were 0.4% and 6.65%. Significant associations between exposure to tizanidine and ciprofloxacin and outpatient physician visits were found for 30 and 14 days (OR 1.59 (95%CI 1.1-2.34), p = 0.016 and OR 1.61 (95%CI 1.17-2.24), p = 0.004). A non-significant trend for increase of risk for hospitalisation was found for all evaluated time periods (OR 1.68 (95%CI 0.84-3.17), OR 1.52 (95%CI 0.63-3.33) and OR 2.19 (95%CI 0.88-5.02).

Conclusion: The interaction between tizanidine and ciprofloxacin is highly relevant both for individual patients and at the population level. Further investigation of the impact of other clinically relevant DDI is necessary to improve patient safety and reduce avoidable health care utilisation.

1. Background and Objectives

Several reports highlighted the importance of potential drug-drug interactions (pDDI) as a risk factor for adverse drug events over the last decades.[1,2] Nevertheless, the impact of DDI on a public health level remains controversial: Rates for hospitalisations due to DDI vary between 0.1% and 6.2%, depending on study size and patient collective.[3,4] Additionally, DDI have been described to be associated with increased length of stay and elevated cost of hospitalisation [5]. However, not all pDDI are clinically relevant and many can be managed safely.[6,7]

Although precautionary measures, such as DDI-alert systems, are well established, co-prescribing of drug combinations that potentially cause severe DDI [6-11], such as tizanidine and ciprofloxacin [12], still occurs. Tizanidine is a central a_2-adrenoceptor agonist with a narrow therapeutic range, which is approved for treatment of spasticity in Switzerland.[13,14] Its metabolism is mainly mediated by cytochrome P450 1A2-isoenzyme. Ciprofloxacin, a quinolone antibiotic, has been shown to be a clinically relevant inhibitor of CYP1A2.[15] In a pharmacokinetic study, ciprofloxacin increased the area under the plasma-concentration curve (AUC) of tizanidine by an average of 10-fold (range 6-fold to 24-fold).[15] Case reports highlight the potential threat to affected patients: adverse reactions such as cardiovascular (e.g. severe hypotension) and CNS-depressive effects (e.g. drowsiness) have been reported.[12,14-16] A recent analysis of the WHOs database on adverse drug reactions (ADR) (Vigibase™) identified 64 tizanidine-related individual cases involving ciprofloxacin, with four being fatal.[17] While severity of the interaction has been well described in single patients, its impact on risk for hospitalisation or outpatient physician visits ("visits") has not yet been examined on a larger scale.

The aim of this study was to investigate the frequency and describe the type of pDDI rated as contraindicated (X) or major (D) using a large claims database in Switzerland. We evaluated the risk for hospitalisation and visits for one contraindicated pDDI identified exemplary. With respect to its contraindication, a relative high number of patients were prescribed tizanidine and ciprofloxacin concomitantly. This particular interaction was selected because of the high clinical relevance.

2. Methods

2.1 Characteristics of the study population

Anonymised claims data was provided by a large health insurance company in Switzerland (Helsana Group). The dataset encompassed 524,797 insured Swiss patients accounting for 22,768,948 drug-prescriptions in 2014 and 2015. Swiss patients (age ≥ 18) with no additional private insurance, who had at least five drug prescriptions within one calendar year were included. All participants were insured at the health insurance company for the entire course of the study period. Participants who died within that period were excluded. The dataset contained records of all health care invoices. Information on prescribed drugs and health care utilisation (e.g. hospitalisation, physician visits), as well as demographic parameters, health insurance status and costs was available for each patient.[18] The representativeness of the study population has been examined (Suppl. 1).

2.2 Frequency and type of interactions

Potential DDI were defined as prescription of two drugs within 7 days. All combinations labelled ‘contraindicated’ (n = 663) and ‘to be avoided’ (n = 1785) in

the Matrix-database were evaluated [Fig. 1]. Matrix is an expert system from the Department of Clinical Pharmacology and Toxicology, University Hospital Zurich, Switzerland, which ranks interactions on severity using a validated decision model.[19] Frequency analyses have been carried out for the year of 2014 and stratification for age, sex and number of different drugs has been performed. Similar results were expected for 2015. Drug classes frequently involved were described and interactions have been grouped with respect to the main potential (adverse) effect. Out of all contraindicated pDDI observed, the combination of ciprofloxacin and tizanidine was chosen for further evaluation.

2.3 Cohort study design

A cohort study was conducted with respect to hospitalisations and visits within 7, 14 and 30 days after starting antibiotic therapy in patients prescribed tizanidine. The study design is illustrated in [Fig. 2]. In contrast to the frequency analysis, exposed and unexposed patients were included from both 2014 and 2015. Exposed patients (ciprofloxacin and tizanidine, n = 199) were compared with a group of patients who were unexposed to ciprofloxacin (and thus to the ciprofloxacin-tizanidine interaction) but were also prescribed tizanidine and an antibiotic with a comparable antibiotic spectrum and indication as ciprofloxacin concomitantly (n = 960).

2.3.1 Definition of exposed and unexposed patients

Exposure was pre-defined as the prescription of tizanidine and ciprofloxacin within 7 days of each other between Feb 2014 and Nov 2015 (n = 321). Of those, only patients with tizanidine prescribed before or on the same day as ciprofloxacin as the first occurrence were included. This definition was chosen to increase the probability

of concurrent exposure as the treatment duration of ciprofloxacin may vary with respect to the indication. If the combination was co-prescribed within 7 days for multiple times in a patient during the study period, only the first occurrence of tizanidine-ciprofloxacin was evaluated (n = 231). The start date of ciprofloxacin was defined as the index date. No ciprofloxacin was allowed to have been prescribed 30 days before the index date. Additionally, no other control antibiotic may have been prescribed either at the index date or up to 7 days before the prescription of tizanidine. This was done to apply the same restrictions as for the unexposed group. The final number of exposed patients analysed was n = 199.

Unexposed patients were prescribed tizanidine together with an antibiotic other than ciprofloxacin within 7 days (n = 1422). Tizanidine had to be prescribed before or at the same day as the antibiotic. If the combination was co-prescribed multiple times within 7 days for a patient during the study period, only the first occurrence of tizanidine-antibiotic (index date) was evaluated and the patient was excluded if co-prescription of antibiotic-tizanidine occurred within 3 months before index date. Ciprofloxacin must not have been prescribed 30 days before or after the index date. Only one antibiotic may have been prescribed at the index date with no antibiotic prescribed up to 7 days before the prescription of tizanidine. Finally, 960 unexposed patients were analysed.

No additional restrictions regarding prescriptions of either tizanidine or antibiotics before or after the index date were made in both groups. The patient inclusion process is displayed in a flowchart (Suppl. 2).

2.3.2 Investigated outcomes

Both hospitalisations ('Hospitalisation', binary) and visits ('Visits', binary and log(count)) were evaluated as adverse outcomes. Hospitalisations were identified using Swiss Diagnosis Related Group-Codes, which are case based lump sums used for the invoice of inpatient hospitalisation services.[20] Visits were identified using invoice codes for outpatient medical treatments.[21] Both visits at the physician's office and home visits by the physician were considered.

2.4 Statistical methods

Data was analysed with R (Version 3.3.1). For dichotomous variables absolute and relative frequencies were calculated. For continuous variables medians and interquartile range (IQR) were provided. Age categories were transformed to a continuous variable by applying a stratified imputation. To disclose associations between two discrete variables, the Fisher exact test was used. Association between a continuous and a discrete variable with two levels were assessed by the Mann-Whitney test. Due to only n = 199 exposed patients, age categories were transformed to a continuous variable by applying a stratified imputation. Multiple regression models were used to evaluate whether there was an association between the concurrent use of ciprofloxacin and tizanidine (exposed) and the evaluated outcomes. Multiple logistic regression adjusting for demographical variables was applied for the binary outcomes of hospitalisation or outpatient physician visit. Odds Ratios were computed. The number of visits was transformed logarithmically, allowing for application of multiple linear regression adjusting for age, sex and number of different drugs prescribed. Model choice was assisted by the Akaike

information criterion (AIC). Power analysis was conducted with STATA (Version 13.1, StataCorp LP). A p-value less than 0.05 was considered statistically significant.

3. Results

3.1 Frequency and type of interactions

Contraindicated pDDI were identified in 0.4% (n = 2119) of patients and D-pDDI were found for 6.65% (n = 34,885) of the study population (n = 524,797). Women were affected more frequently by both X- and D-interactions than men (X-pDDI: 0.34% for men, 0.45% for women; D-pDDI 5.8% and 7.3%). The frequency of patients affected by interactions increased both with age (X-pDDI: 0.24% for age 25-34, 0.61% for age 75-84; D-pDDI 3.6% and 9.9%) and the number of different drugs prescribed per year (X-pDDI: 0.16% for 6-10 drugs, 1.67% for ≥16 drugs; D-pDDI 4.29% and 21.5%). Drug classes most frequently involved were propulsives (A03F, 16.2%), macrolides, lincosamides and streptogramins (J01F, 13.9%) and antimycotics for systemic use (J02A, 8.3%) for X-interactions and NSAIDs (M01A, 17.4%), antithrombotic agents (B01A, 13.11%) and hypnotics/sedatives (N05C, 13.1%) for D-labelled interactions. When evaluated with respect to potential (adverse) effect of both X- and D-DDI, highest frequencies of affected patients were found for interactions increasing the risk of bleeding (n = 15077, 32.7%), causing CNS-depressing effects (n= 11847, 25.7%) and augmenting risk for cardiac toxicity (n = 9798, 21.3%).

3.2 Cohort study

Descriptive statistics are summarised in Table 1. A noteworthy discrepancy between the groups was found for the age variable. The composition of antibiotic prescriptions received by unexposed patients at the index date involved multiple groups of antibacterials: penicillins with/without clavulanic acid (n = 354, 36.9%), macrolides (n = 154, 16%), fosfomycin (n = 145, 15.1%), other fluoroquinolones (n = 101, 10.5%), oral cephalosporins (n = 79, 8.2%), sulfamethoxazole/trimethoprim (n = 61, 6.4%), nitrofurantoin (n = 36, 3.8%) and tetracyclines (n = 30, 3.1%).

Risk for at least one visit after the onset of ciprofloxacin significantly increased for 30 and 14 days by as much as 1.6-fold. No significant association was found for 7 days. No relevant increase in the number of visits were found for all three observation periods (Table 2).

Exposure to concomitant tizanidine and ciprofloxacin was associated with a non-significant but relevant increase in risk for hospitalisation within 7, 14 and 30 days after prescription of the antibiotic by 1.52 to 2.19-fold. A power analysis for the 30-day timeframe (two-sample proportion tests corrected for allocation ratio (0.2070, n = 1159), sig.-level = 0.05) revealed a power of 0.4389. This indicates that the study did not have enough power to detect the difference between the two groups with respect to hospitalisation.

No significant differences in frequency of hospitalisations and visits for 7, 14 and 30 days before and after the index date were seen (data not shown).

4. Discussion

Our results illustrate the relevance of the interaction between tizanidine and ciprofloxacin on a public health level: the probability of a visit increased significantly by 1.6-fold, if tizanidine and ciprofloxacin were prescribed concomitantly (30 and 14 days).

4.1 Outpatient physician visits

Switzerland has approximately 6.7 million inhabitants above the age of 18 years. Given the frequency of 0.0322% for the ciprofloxacin-tizanidine interaction in our study population we extrapolate that 2157 patients may be affected in Switzerland annually. According to our study 64.8% of those would experience at least one visit within 14 days (n = 1398). Assuming the avoidance of the interaction (unexposed: 52.9% visits) roughly 256 patients may be prevented from having a visit.

Additional visits do not only have economic consequences; they first and foremost indicate an impaired medical condition. In contrast to hospitalisations, visits have rarely been studied as adverse outcomes in the literature. It can be assumed that in many cases patients may first contact their attending physician when they experience DDI-related adverse reactions or feel unwell during the therapy rather than requiring hospitalisation; therefore, visits are a key piece of the puzzle when studying the impact of DDI. *Bourgeois et al*. reported a significant trend of increase in ADE-related visits to outpatient clinics in the US from 9.1 to 16.9 visits per 1000 persons between 1995 and 2005.[22] Emergency department visits have not been evaluated due to low incidence. Fortunately, the interaction can be avoided: For several indications, ciprofloxacin can be replaced by another antibiotic that does not carry the risk of a pharmacokinetic interaction. For tizanidine, pausing treatment

during antibiotic therapy or substituting the drug depending on patients' individual indication are two possible options. As underlying medical conditions requiring tizanidine and acute antibiotic therapy were expected to increase the risk for hospitalisations and visits, confounding for indication was addressed by a control group (unexposed) receiving antibiotics with a comparable spectrum and indication as ciprofloxacin. Such cohort studies using negative control precipitants are accepted study designs to investigate health effects of pDDI.[23]

Several classes of oral antibiotics were combined to form an adequate control group. Due to the small number of patients receiving tizanidine and other quinolones and the broader spectrum of indications for ciprofloxacin compared to other quinolones we decided against a control group only comprising quinolones.

Because pharmacokinetic studies indicate a rapid increase in tizanidine exposure after initiation of concomitant ciprofloxacin therapy, possible adverse reactions requiring health-care utilisation were expected to occur within a short timeframe. Therefore, 7, 14 and 30 days were chosen, allowing for the evaluation of a development of altered risk for adverse outcomes. Interestingly, the weakest association between exposure and visits was observed for 7-days (OR 1.12, 95%CI 0.81-1.53). The reasons for this remain speculative: Overlapping effects of the underlying disease (antibiotic therapy) may have been more common in the first days. Additionally, severe adverse reactions in susceptible patients may have appeared rapidly, possibly requiring hospitalisation rather than visits.

4.2 Hospitalisation

An increased risk for hospitalisation by as much as 2.19-fold (95%CI 0.88-5.02, p = 0.07) shortly after the start of ciprofloxacin therapy in tizanidine patients identifies a

dangerous trend. As expected, the highest risk for hospitalisation was found within 7 days.

The clinical relevance of other pDDI was evaluated for different combinations, such as statins and macrolides: While some studies found an increased risk for hospitalisations[24-27], others could not demonstrate an association.[28]

4.3 Frequency and type of interactions

We found an overall frequency of contraindicated interactions of 0.4% and a considerably higher rate of 6.65% for patients prescribed at least one major combination (n = 524,797). Such high rates of severe interactions highlight the need for ongoing implementation of DDI-alerting systems to prevent prescribing of potentially harmful combinations.

Analysis of the frequency of interactions have been carried out in various studies. The reported frequencies depend on the type of interactions studied, the definition of interactions, the setting of the project (e.g. claims data, clinical study) and the patient collective.[11] An analysis of contraindicated pDDI in Swiss claims data with the focus on specialisation of physicians causing those pDDI using the defined daily dose method revealed rather similar rates (0.4% in females and 0.5% in males)[29] compared to our study. We therefore consider our approach of using a 7-day timeframe both a pragmatic and reasonable method to estimate overall frequencies of multiple pDDI in large datasets.

Timeframe methods are commonly used in the literature to identify pDDI.[8,9,11,30] We decided to use a short timeframe of 7 days to increase the probability of concomitant intake. In line with findings from other claims-data based studies[8-11] we found higher frequencies of pDDI in females, with increasing age and number of different drugs.

As the studied population was older with more female patients compared with the Swiss population (Suppl. 1), frequencies of pDDI may be overestimated when generalised to Switzerland. The most frequent possible adverse effects of pDDI in our study were risk of bleeding, CNS-depression and cardiac toxicity, which was comparable with previous findings.[8, 9]

4.4 Limitations

The project has several limitations. The calculation of pDDI was made under the assumption of instant drug intake. Formally contraindicated combinations may be prescribed intentionally as off-label treatment in exceptional cases. Information on over the counter medication (OTC) and prescriptions during hospitalisation was lacking in the dataset. As interactions involving such medication could not be taken into account, the frequency of the interactions may be underestimated. Because of the conservative approach of using a 7-day timeframe to define pDDI, the frequency of pDDI may have been underestimated, especially because pDDI between a continuous therapy and acute prescriptions may have been missed.

Although susceptibility to confounding by indication can be reduced by using a control group in the cohort study, differences between the groups regarding unmeasured covariates (e.g. comorbidities, prior healthcare utilisation) cannot be ruled out. No information on actual admission diagnoses for hospitalisation or reasons for visits were available. Because of comparison with the control group, increased risk is believed to be largely attributable to ciprofloxacin and thus the interaction. However, no causal relationship can be established.

5. Conclusion

The example of tizanidine and ciprofloxacin demonstrates that severe DDI are not only crucial for individual patients but may also have high relevance on a public health level by increasing the risk for health care utilisation. As this interaction can be bypassed by therapy adjustment, adverse outcomes can be avoided. With societies growing older and rising numbers of patients suffering from multimorbidity and receiving polypharmacy, evaluating the impact of DDI from a public health perspective is of increasing importance.

Compliance with Ethical Standards

Ethical Approval Harmlessness of the study was attested by the Cantonal Ethics Committee of Zurich, although no formal ethical approval was required due to Swiss Law. The concept of anonymisation was approved by the Cantonal Data Security Officer.

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Conflict of Interest The authors declare no conflict of interest.

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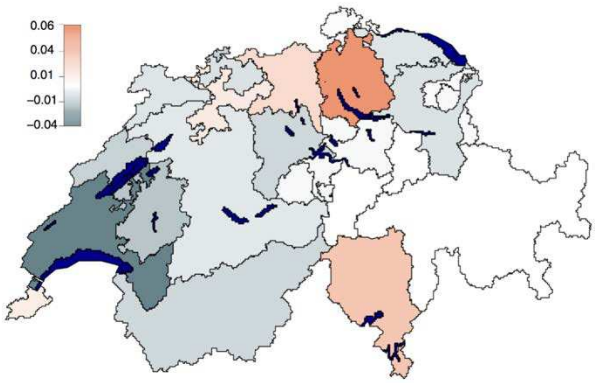
Supplementary information 1: Demographics and representativeness of the study population

Method:

Data from the Swiss Federal Statistical Office (FSO) (https://www.bfs.admin.ch/bfs/en/home/fso/swiss-federal-statistical-office.html.) was used to obtain information on the characteristics of the Swiss population. Demographic characteristics have been compared using 95%CI (Wilson) and the Chi^2 test and the relevance of the deviations has been assessed.

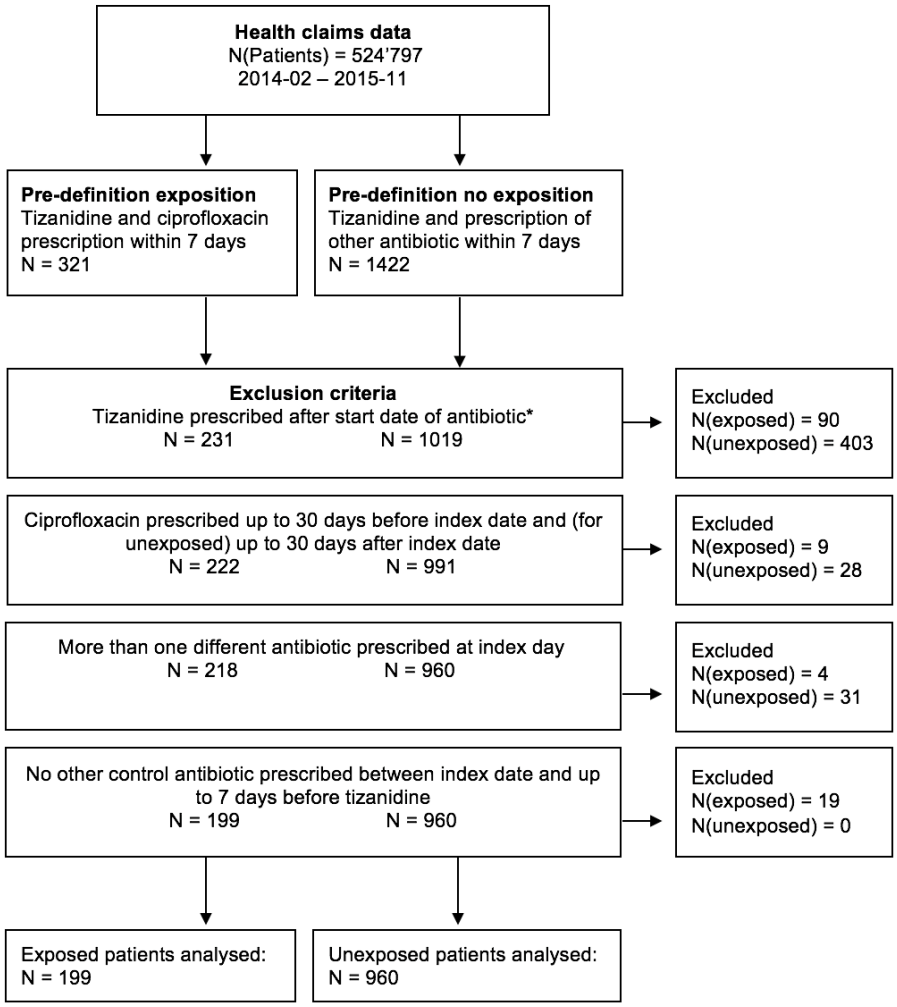
Results:

524,797 patients were included in the study dataset (Population of Switzerland n = 8,237,666 in 2014). The Chi^2 test revealed that the distribution of age categories was different between the datasets ($p < 0.001$). The study patients were older, showing the highest relative frequency for the age category of 65-69 (9.7%), whereas for the Swiss population the highest frequency was found for the age category of 45-49 (8.0%). A higher proportion of women was found in the study data compared with the Swiss population (58.7% (95%CI 58.6%-58.9%) vs. 50.6% (95%CI 50.5%-50.6%). Patients from all cantons were represented in the study dataset. Relative difference of proportions of patients living in the different cantons of Switzerland is presented in Suppl. Fig. 1. For most cantons the relative difference was small. The largest deviations were found for the cantons of Zurich (5.7%, slightly overrepresented) and Vaud (-3.7%, slightly underrepresented).



Suppl. Fig. 1: **Relative differences in canton of residence** for 2014 between study dataset and Swiss population

Supplementary information 2: Inclusion process



Suppl. 2: Process of inclusion of patients into exposed and unexposed groups *In case an unexposed patient received the combination of an antibiotic prescribed before tizanidine within 7 days earlier during the evaluated years, the combination must have been prescribed at least 3 months before the index date

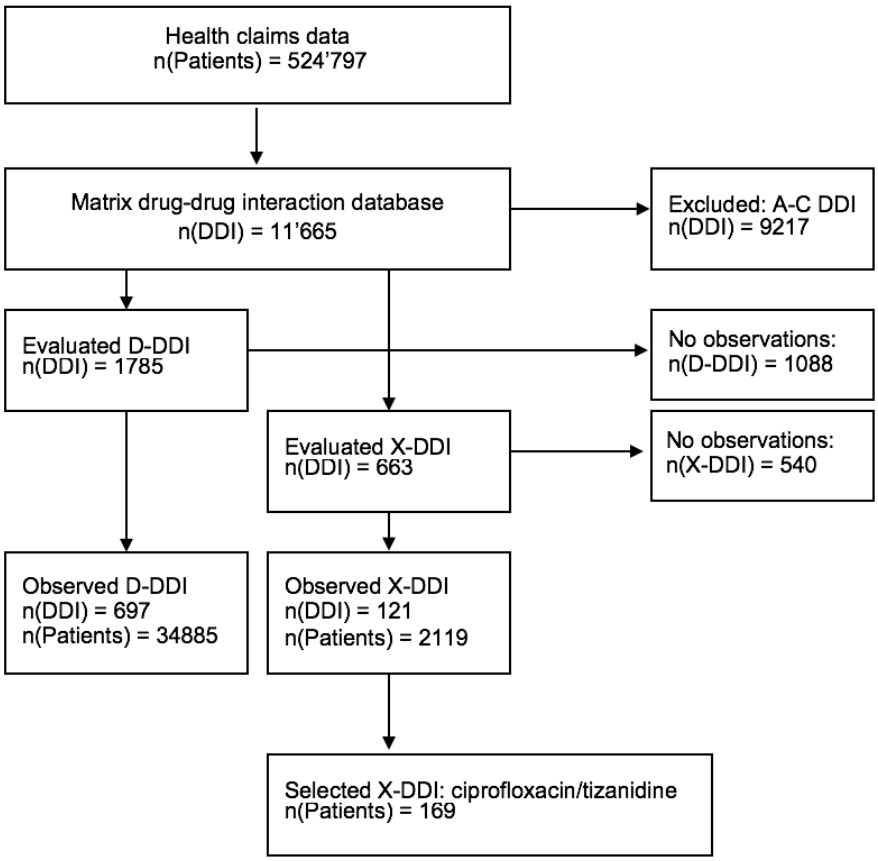


Fig. 1: Flowchart: Evaluation of the frequency of pDDI in Swiss claims data DDI = drug-drug interaction, A-X = severity grading according to validated decision model, N(DDI) = Number of different pDDI, n(Patient) = Number of patients prescribed at least one of the specified X- or D-pDDI in 2014

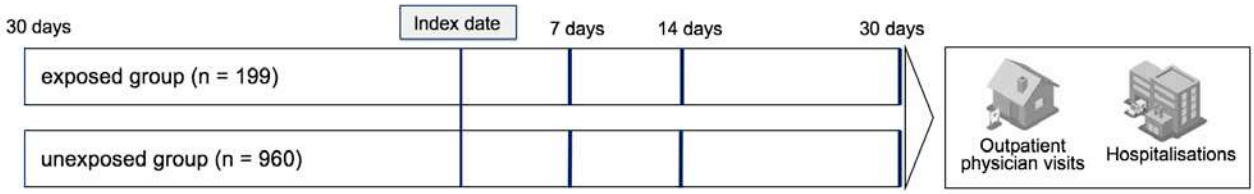


Fig. 2: **Cohort study design.** Tizanidine patients were prescribed antibiotic therapy at the index date with the exposed group being prescribed ciprofloxacin and the unexposed group being prescribed an antibiotic other than ciprofloxacin. Outcomes (outpatient physician visits, hospitalisations) were evaluated 7, 14 and 30 days after the index day.

Table 1: **Descriptive statistics for exposed (ciprofloxacin and tizanidine) and unexposed (other antibiotic and tizanidine) groups**

	Exposed group (n = 199)		***Unexposed group (n = 960)***		
	abs. freq	**rel. freq**	**abs. freq**	**rel. freq**	**p-value**
Sex					
male	66	33.2%	277	28.9%	0.26
female	133	66.8%	683	71.1%	
Age					
Median	58.3		54.4		0.06
IQR	(46.5-69.4)		(41.8-68)		
Number of different Drugs*	20		18		0.44
Median	(13-26)		(12-27)		
IQR					
Package strength Tizanidine**					
2 mg tab	61	30.7%	296	30.8%	0.59
4 mg tab	114	57.3%	572	59.7%	
6 mg MR caps	23	11.6%	75	7.8%	
12 mg MR caps	-		7	0.7%	
combination multiple strengths	1	0.5%	10	1.0%	

abs. freq: absolute frequency, rel. freq: relative frequency

*Number of different drugs prescribed in the year of index date

**Package(s) last prescribed before the index date

Table 2: **Results of multiple logistic and linear regression analysis for hospitalisations and outpatient physician visits.**

Outcome (Y)	Y = 1/n (exposed; unexposed)	Age	SexM	Number of drugs	Exposure	
Hospitalisation (0/1) 30 days						
ß	13/199;	0.02	0.47	0.03	0.52	
OR	36/960	1.02	1.6	1.03	**1.68**	
95%CI(OR)		1.00-1.04	0.86-2.87	1.01-1.06	0.84-3.17	
p-value		0.02	0.12	0.005	0.13	
Hospitalisation (0/1) 14 days						
ß	8/199;	0.017	0.54	0.04	0.42	
OR	24/960	1.02	1.72	1.04	**1.52**	
95%CI(OR)		0.995-1.04	0.81-3.52	1.01-1.07	0.63-3.33	
p-value		0.13	0.14	0.01	0.32	
Hospitalisation (0/1) 7 days						
ß	8/199;	0.014	0.49	0.026	0.78	
OR	17/960	1.014	1.63	1.027	**2.19**	
95%CI(OR)		0.99-1.04	0.7-3.64	0.99-1.06	0.88-5.02	
p-value		0.27	0.24	0.12	0.07	
Visit (0/1) 30 days	155/199; 658/960					
ß		0.006	0.172	0.067	0.46	
OR		1.01	1.19	1.07	**1.59**	
95%CI(OR)		0.998-1.01	0.89-1.6	1.05-1.09	1.1-2.34	
p-value		0.15	0.25	<0.001	**0.016**	*
Visit (0/1) 14 days						
ß	129/199;	0.002	0.21	0.04	0.48	
OR	508/960	1.00	1.24	1.05	**1.61**	
95%CI(OR)		0.99-1.01	0.95-1.61	1.03-1.06	1.17-2.24	
p-value		0.64	0.11	<0.001	**0.004**	**

Visit (0/1)					
7 days					
ß	80/199;	0.005	0.2	0.03	0.11
OR	353/960	1.00	1.22	1.03	**1.12**
95%CI(OR)		0.998-1.01	0.94-1.59	1.02-1.04	0.81-1.53
p-value		0.19	0.14	<0.001	0.50
Visit (log(count))					
30 days					
ß		0.001	0.12	0.02	0.07
exp(ß)		1.00	1.13	1.02	**1.07**
95%CI(exp(ß))		0.999-1.003	1.05-1.22	1.02-1.025	0.98-1.17
p-value		0.22	0.001	<0.001	0.13
Visit (log(count))					
14 days					
ß		0.0005	0.088	0.013	0.065
exp(ß)		1.00	1.09	1.013	**1.07**
95%CI(exp(ß))		0.999-1.002	1.02-1.16	1.01-1.016	0.99-1.15
p-value		0.61	0.008	<0.001	0.10
Visit (log(count))					
7 days					
ß		0.0008	0.055	0.007	0.002
exp(ß)		1.00	1.06	1.01	**1.00**
95%CI(exp(ß))		0.999-1.002	1.00-1.11	1.00-1.01	0.94-1.07
p-value		0.29	0.04	<0.001	0.96

OR = Odds Ratio, 95%CI = 95% Confidence interval, *p < 0.05, ** p< 0.01